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(19)

(54) COMPOSITIONS CONTAINING SUBSTITUTED BIS-CHROMONYL COMPOUNDS

(71) We, FISONS LIMITED, a British Company of Fison House, 9 Grosvenor Street, London W1X 0AH, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

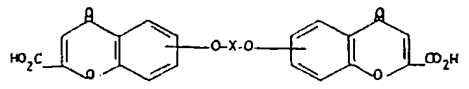
This invention concerns pharmaceutical compositions.

In our British Patent No. 1,144,905 there are described and claimed certain substituted bis - chromonyl compounds and compositions containing them which may be administered orally, parenterally or by inhalation in the treatment of various conditions, including asthma.

In our British Patent Application No. 6911/72 (Serial No. 1,423,985) we describe and claim certain compositions of the compounds claimed in British Patent No. 1,144,905, which compositions are of use in the treatment in man of disorders of the alimentary tract, in which disorders allergic or immune reactions play a contributory part.

We have now found that further compounds may also be used in the treatment of such disorders, and that improved results are obtained at higher dosage rates than those hitherto described.

Accordingly, this invention provides a composition suitable for the administration of a compound of the formula:



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(wherein X represents a polymethylene chain containing from 3 to 7 carbon atoms, which chain may be substituted by a hydroxy group) or a therapeutically acceptable salt, alkyl C 1 to 10 ester, mono - alkyl C 1 to 10 amide, di - alkyl C 1 to 10 amide or unsubstituted amide thereof, to a patient having a disorder of the alimentary tract, in which disorder allergic or immune reactions play a contributory part, the composition being in unit dosage form containing more than 250 mg and up to 1000 mg of active ingredient.

Suitable pharmaceutically acceptable salts include, for example, ammonium salts, alkali metal salts (e.g. sodium, potassium and lithium), alkaline earth metal salts (e.g. magnesium and calcium), and salts with organic amines (e.g. mono-, di- or tri-alkyl C 1 to 6 amines, piperidine, and trialkanol C 1 to 6 amine salts). Esters which may be mentioned include simple alkyl esters (e.g. methyl, ethyl, propyl, isopropyl, butyl and tertiary butyl esters) and amides which may be mentioned include simple amides (for example amides with ammonia and lower alkylamines such as methylamine, ethylamine etc.).

Where the condition affects the rectum the administration may be by way of suppository, enema or other conventional vehicle for administration to the rectum. Where the condition affects another part of the alimentary tract then the administration may be orally, for example as a tablet, dragée, lozenge, powder, solution, suspension or syrup. Syrups, solutions, suspensions and powders may conveniently be presented contained in a hard or soft capsule as appropriate.

In order to produce suitable compositions the drug is worked up with inorganic or organic pharmaceutically acceptable adjuvants or excipients. Examples of such adjuvants are:

for tablets and dragées: binders, for example gelatin, polyvinylpyrolidone or cellulosic materials, e.g. microcrystalline cellulose and methyl cellulose; disintegrating agents, for example starches, e.g. maize starch; stabilisers, e.g. against hydrolysis of the active ingredients; flavouring agents, for example sugars such as sucrose or lactose; fillers; stearates; and inorganic diluents, e.g. talc,

for syrups, suspensions or dispersions: a liquid vehicle in which the active ingredients may be dissolved or suspended, e.g. water; and suspending agents, e.g. cellulose derivatives, gums etc.,

for powders: diluents, e.g. lactose; glidants, e.g. stearates; inorganic materials, e.g. silica or talc; stabilisers and dispersing agents,

for suppositories: natural or hardened oils, waxes etc: a large number of proprietary emulsifying bases are available and are suitable for use in suppositories; these include 'Witepsol' (Registered Trade Mark) bases, consisting of hydrogenated triglycericles of lauric acid with added monoglycerides; and 'Massupol' bases, which consist of glyceryl esters of lauric acid with a very small amount of glyceryl monostearate,

For enemas: water, sodium chloride, buffers etc.

The composition may also contain further adjuvants, for example a composition for forming tablets may contain lubricants and glidants to assist in tabletting, e.g. magnesium stearate, or wetting agents to assist in granulation, e.g. dioctyl sodium sulphosuccinate. The composition may also if desired contain a pharmaceutically acceptable dye or colourant, and may, if desired, be coated using conventional film or sugar coating techniques.

If desired the composition may be formulated in sustained release form, e.g. by coating the drug particles themselves or granules thereof made with, for example, sucrose and of a size up to 2 mm in diameter with a layer of, e.g. beeswax, Carnauba wax, stearic or palmitic acids, cetyl alcohol or similar substances which could be expected to be slowly dissolved or digested or to act as semi-permeable membranes through which the drug can diffuse when the preparations are ingested. The composition may contain drug particles or granules which are uncoated in admixture with particles or granules having one or more coats of the coating medium, and may be in the form of a capsule containing the particles or granules or alternatively a tablet, for which other adjuvants may be required, such as glidants or lubricants. The drug may be administered as an enteric coated composition to make the drug available at the appropriate part of the gastro-intestinal tract. This may be achieved by coating the tablet with a continuous film of material which is resistant and impermeable to gastric secretions, but which is susceptible to intestinal secretions. Typical film materials are shellac and its derivatives and cellulose acetate phthalate.

The drug may also be formulated as an aqueous or predominantly aqueous, e.g. a water: chloroform (400:1), solution containing from 0.001 to 10.0% by weight of the drug. The free acids of formula I may conveniently be administered as an aqueous suspension containing from 0.1 to 10%, e.g. about 2% by weight of the drug.

The dosage to be administered will of course vary with the condition to be treated, with its severity and location, and with the patient to be treated. However, in general, a total daily dosage of between 250 and 4000 mg of active ingredient is found to be satisfactory. Generally it is preferred to administer between 250 and 2000 mg of active ingredient per day, a more preferred daily dosage being between 250 and 800 mg. The daily dosage is preferably administered an appropriate number of times per day (e.g. 2 to 4) in unit dosage form preferably containing more than 250 but less than 500 mg of active ingredient. The administration preferably takes place about 30 minutes before the patient takes food.

Conditions which may be treated by the method of the present invention include Crohn's disease (a condition of the small, and sometimes also of the large, intestine), atrophic gastritis (a condition of the stomach), ulcerative colitis (a condition of the large intestine and sometimes the small intestine), proctitis (a condition of the rectum and lower large intestine), coeliac disease (a condition of the small intestine), regional ileitis (a regional inflammatory condition of the terminal ileum), peptic ulceration (a condition of the stomach and duodenum), gastro-intestinal allergy (e.g. milk, gluten and other food allergy), and irritable bowel syndrome. As a further condition there may be mentioned gastro-intestinal bleeding induced by the administration of an anti-inflammatory agent, for example indomethacin or aspirin.

Specific examples of the group X are groups of the formula

$$-(CH_2)_5- \text{ and } -CH_2CHOHCH_2-.$$

The chain —O—X—O— may link different or corresponding positions on the chromone nuclei.

Specific compounds which may be used in accordance with the present invention are:—

1,3 - Bis(2 - carboxychromon - 5 - yloxy)-propane,
1,3 - Bis(2 - carboxychromon - 5 - yloxy) - 2 - hydroxypropane,
1,4 - Bis(2 - carboxychromon - 5 - yloxy)-butane,
1,5 - Bis(2 - carboxychromon - 5 - yloxy)-pentane,
1,6 - Bis(2 - carboxychromon - 5 - yloxy)-hexane,
1,4 - Bis(2 - carboxychromon - 5 - yloxy) - 2,3 - dihydroxybutane,
1,4 - Bis(2 - carboxychromon - 5 - yloxy) - 2 - hydroxybutane,
1,5 - Bis(2 - carboxychromon - 7 - yloxy)-pentane,
1 - (2 - Carboxychromon - 5 - yloxy) - 3 - (2 - carboxychromon - 7 - yloxy) - 2 - hydroxypropane,
1 - (2 - Carboxychromon - 5 - yloxy) - 5 - (2 - carboxychromon - 7 - yloxy)-pentane,

1,5 - Bis(2 - carboxychromon - 8 - yloxy)-pentane,
1,5 - Bis(2 - carboxychromon - 6 - yloxy)-pentane,
1,3 - Bis(2 - carboxychromon - 7 - yloxy) - 2 - hydroxypropane,
1,3 - Bis(2 - carboxychromon - 6 - yloxy) - 2 - hydroxypropane,
1 - (2 - Carboxychromon - 5 - yloxy) - 3 - (2 - carboxychromon - 6 - yloxy) - 2 - hydroxypropane, and
1 - (2 - Carboxychromon - 5 - yloxy) - 3 - (2 - carboxychromon - 8 - yloxy) - 2 - hydroxypropane.

The above mentioned compounds may of course be used in the form of their pharmaceutically acceptable, e.g. their di-sodium, di-potassium, calcium, magnesium or dipiperidine salts. They may also be used in the form of their di-ethyl esters, or of their simple amides derived from ammonia. We prefer to use the compounds 1,3 - bis(2 - carboxy - chromon - 5 - yloxy) - 2 - hydroxypropane, or 1,3 - bis(2 - carboxy - chromon - 7 - yloxy) - 2 - hydroxypropane, or a pharmaceutically acceptable salt of either.

The invention is illustrated, but in no way limited by the following Examples.

Example 1

An enema was produced by admixing the following components:

Sodium Cromoglycate BP	0.50 g
Sodium Chloride BP	0.44 g
Sodium Phosphate BP	1.91 g
Sodium Acid Phosphate BP	0.21 g
Purified Water BP	to 100 ml

Methyl cellulose or other agents may be added to aid retention of the solution in the bowel.

Example 2

Suppositories were produced from the following components:

Sodium Cromoglycate BP	0.275 g
Witepsol base S55	q.s

Water-miscible suppositories with a polyethylene glycol base in place of the Witepsol base were also produced.

Example 3

An oral liquid was produced by admixing the following components:

Sodium Cromoglycate BP	5.0 g
Sucrose BP	50.0 g
Methyl - p - hydroxybenzoate BP	0.18 g
Propyl - p - hydroxybenzoate BP	0.02 g
Flavouring and colouring agents	q.s
Purified Water BP	to 100 ml

This was then divided into 10 equal unit doses of 10 ml each.

Example 4

Micronised Sodium Cromoglycate was moistened with water up to a total moisture content of 25% w/w, then granulated, dried, and sieved. In this form, 275 mg unit doses were filled into size 0 hard gelatin capsules.

Example 5

Cromoglycic acid was formulated as a suspension as follows:

Cromoglycic acid	10.0 g
Sodium carboxymethyl cellulose (Edifas B50")[1]	2.0 g
Sorbitol solution BPC	10.0 g
Benzoic Acid BP	0.1 g
Saccharin sodium BP	0.05 g
Flavouring and colouring agents	q.s
Purified Water BP	to 100 ml

[1]—Edifas is a Registered Trade Mark.

This was then divided into 20 equal unit doses of 5 ml each.

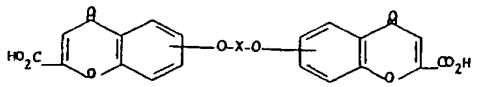
Example 6

A tablet disintegrable in the stomach was formulated as follows:

Sodium Cromoglycate BP	500 mg
Sodium Bicarbonate BP	375 mg
Maize Starch BP	89 mg
Talc BP	40 mg
Purified water BP	q.s

WHAT WE CLAIM IS:—

1. A composition suitable for the administration of a compound of the formula:



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(wherein X represents a polymethylene chain containing from 3 to 7 carbon atoms, which chain may be substituted by a hydroxy group) or a therapeutically acceptable salt, alkyl C 1 to 10 ester, mono - alkyl C 1 to 10 amide, dialkyl C 1 to 10 amide or unsubstituted amide thereof, to a patient having a disorder of the alimentary tract, in which disorder allergic or immune reactions play a contributory part, the composition being in unit dosage form containing more than 250 mg and up to 1,000 mg of active ingredient.

2. A composition as claimed in claim 1 wherein the active ingredient is an ammonium salt, an alkali metal salt, an alkaline earth metal salt or a salt with an organic amine.

3. A composition as claimed in claim 2 wherein the salt is a sodium salt.

4. A composition as claimed in any of claims 1 to 3 wherein X in the active ingredient represents 2 - hydroxytrimethylene.

5. A composition as claimed in claim 3 and claim 4 wherein the active ingredient is the disodium salt of 1,3 - bis(2 - carboxy - chromon - 5 - yloxy) - 2 - hydroxypropane.

6. A composition as claimed in any of claims 1 to 5 in the form of a tablet, dragée, lozenge, powder, solution, suspension, syrup, suppository or enema.

7. A composition as claimed in any of claims 1 to 6 which contains more than 250 but less than 500 mg of active ingredient.

8. A composition as claimed in any of claims 1 to 7 and substantially as described hereinbefore with reference to the Examples.

F. MURPHY,
Chartered Patent Agent,
Agent for the Applicants,
Fisons Limited,
Fison House,
Princes Street,
Ipswich, Suffolk IP1 1QH.

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